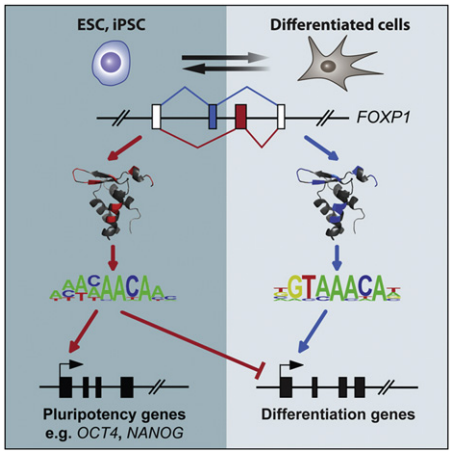
In This Issue

Cell



Splicing Up ES Cell Pluripotency

PAGE 132

Gabut et al. identify a splicing switch that leads to an ESC-specific form of the transcription factor FOXP1, with an altered DNA-binding domain. This isoform stimulates expression of pluripotency genes, represses differentiation genes, and is also required for efficient reprogramming.

Linking mTOR, *let-7*, and Diabetes

PAGE 81

Connecting cellular energy sensing with type 2 diabetes (T2D), Zhu et al. show that muscle-specific overexpression of the *let-7* miRNA-binding protein Lin28 ameliorates insulin resistance and glucose tolerance in mice via upregulation of mTOR signaling. Genome-wide association studies reveal that *let-7* target genes are enriched for SNPs associated with T2D, extending the relevance of these findings to human disease.

Making Translocation Spots Hot

PAGE 95 and PAGE 107

Aberrant fusions between the *c-myc* and *IgH* loci are frequently associated with B-cell lymphoma. In this issue, Klein et al. and Chiarle et al. report high-throughput techniques to investigate how these oncogenic rearrangements occur. By analyzing the repair of inducible DNA double-strand breaks in millions of primary B cells, the authors find that AID activity, chromosome topology, and transcription all conspire to increase the probability of translocation. The findings provide a molecular understanding of translocation hot spots.

DNA Repair Complex Meets Pluripotency Factors

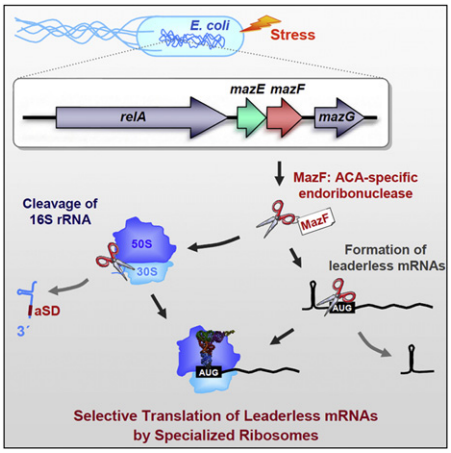
PAGE 120

Fong et al. uncover a stem cell-selective function of a DNA repair complex comprising XPC, RAD23B, and CETN2. This complex coactivates Oct4/Sox2-directed transcription of key pluripotency genes and is important for stem cell maintenance and reprogramming.

Remodeling Ribosomes under Stress

PAGE 147

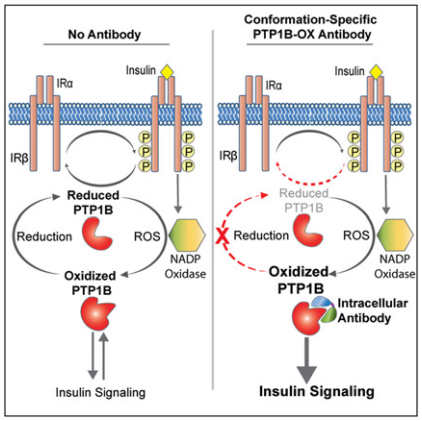
Vesper et al. show that, when under stress, *E. coli* generates functionally specialized ribosomes by truncating 16S rRNA with the endoribonuclease MazF. Moreover, MazF specifically removes 5′UTRs of distinct transcripts to form leaderless mRNAs, which are selectively translated by the altered ribosomes to adjust the translational program in response to stress.



Timed Triggers for Crossovers

PAGE 158

The timely resolution of DNA recombination intermediates is essential for chromosome segregation. Matos et al. show that the activation of two crossover-promoting endonucleases is temporally coordinated with cell-cycle progression to enable the specialized meiotic and mitotic chromosome segregation programs. In meiosis, the nucleases are hyperactivated to promote crossovers, whereas in mitosis, their activities are restrained to favor noncrossover products.



Targeting Reversible Oxidation

PAGE 185

The phosphatase PTP1B regulates insulin and leptin signaling. Haque et al. identify an antibody that selectively recognizes and stabilizes the oxidized, inactive form of PTP1B to promote insulin signaling. The findings indicate that the targeting of oxidized PTP1B is a promising therapeutic approach for diabetes and obesity.

Fatty Acids Congeal Signaling Pathways

PAGE 173

What are the molecular mechanisms behind the ill effects of a high-fat diet? Holzer et al. provide evidence that saturated fatty acids (FA) trigger stress signaling and insulin resistance through their effects on membrane fluidity. Saturated FA, but not unsaturated FA, induce clustering of c-Src into membrane subdomains, which in turn, leads to JNK signaling and resistance to insulin. The findings provide a new model for how membrane composition can trigger different signaling cascades, distinct from a ligand-sensing mechanism.

Channel Gating by Coincidence

PAGE 199

G protein-gated potassium channels control electrical excitability in cells in response to G protein activation and the signaling lipid PIP_2. Whorton and MacKinnon report structures of wild-type and constitutively active mutant channels, providing mechanistic insights into multiligand regulation of channel gating. Their findings reveal that, in the absence of PIP2, G proteins appear to open only one of two sequential gates, whereas the presence of both molecules opens both gates, leading to ion conduction.

Stopping Autophagy on a Dime

PAGE 223

Liu et al. report a small-molecule inhibitor of autophagy that blocks two ubiquitin-specific peptidases. Using the inhibitor, Liu et al. elucidate a regulatory pathway linking Beclin1 and p53 that is controlled by ubiquitination. As reduced levels of Beclin1 lead to reduced p53, these findings provide insights into how Beclin1 functions as a tumor suppressor.

New Model for Autism Treatment

PAGE 235

Peñagarikano et al. report that mice lacking the neurexin *Cntnap2*, a gene strongly associated with autism and related neurodevelopmental disorders, exhibit striking neuropathological and behavioral parallels to humans with mutations in the equivalent gene. As in human autism patients, the repetitive, but not the social behavioral, deficits of the mice are rescued by the drug risperidone, suggesting promise for the model in facilitating the identification of new therapies.

Dynamin Powerstrokes

PAGE 209

The dynamin GTPase mediates the release of clathrin-coated vesicles from the plasma membrane by assembling into collars around the necks of invaginated coated pits. Chappie et al. combine cryo-EM, X-ray diffraction, and crosslinking data to describe the structure and topology of assembled dynamin collars, suggesting that energy from dimerization and GTP hydrolysis is converted into large structural movements that drive membrane fission.